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S2	129	S1 AND PHENOTYP?
S3	39	S2 AND HNRNP(W)A1
S4	22	RD (unique items)

13592700 BIOSIS NO.: 200200221521
hnRNP A1 **nucleocytoplasmic shuttling activity is required for normal myelopoiesis and BCR/ABL leukemogenesis.**
AUTHOR: Iervolino Angela; Santilli Giorgia; Trotta Rossana; Guerzoni Clara; Cesi Vincenzo; Bergamaschi Anna; Gambacorti-Passerini Carlo; Calabretta Bruno; Perrotti Danilo(a)
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JOURNAL: Molecular and Cellular Biology 22 (7):p2255-2266 April, 2002
MEDIUM: print
ISSN: 0270-7306
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **hnRNP A1** is a nucleocytoplasmic shuttling heterogeneous nuclear ribonucleoprotein that accompanies eukaryotic mRNAs from the active site of transcription to that of translation. Although the importance of **hnRNP A1** as a regulator of nuclear pre-mRNA and mRNA processing and export is well established, it is unknown whether this is relevant for the control of proliferation, survival, and differentiation of normal and transformed cells. We show here that **hnRNP A1** levels are increased in myeloid progenitor cells expressing the p210BCR/ABL

oncoprotein, in mononuclear cells from chronic myelogenous leukemia (CML) blast crisis patients, and during disease progression. In addition, in myeloid progenitor 32Dcl3 cells, BCR/ABL stabilizes **hnRNP A1** by preventing its ubiquitin/proteasome-dependent degradation. To assess the potential role of **hnRNP A1** nucleocytoplasmic shuttling activity in normal and leukemic myelopoiesis, a mutant defective in nuclear export was ectopically expressed in parental and BCR/ABL-transformed myeloid precursor 32Dcl3 cells, in normal murine marrow cells, and in mononuclear cells from a CML patient in accelerated phase. In normal cells, expression of this mutant enhanced the susceptibility to apoptosis induced by interleukin-3 deprivation, suppressed granulocytic differentiation, and induced massive cell death of granulocyte colony-stimulating factor-treated cultures. In BCR/ABL-transformed cells, its expression was associated with suppression of colony formation and reduced tumorigenic potential in vivo. Moreover, interference with **hnRNP A1** shuttling activity resulted in downmodulation of C/EBPalpha, the major regulator of granulocytic differentiation, and Bcl-XL, an important survival factor for hematopoietic cells. Together, these results suggest that the shuttling activity of **hnRNP A1** is important for the nucleocytoplasmic trafficking of mRNAs that encode proteins influencing the **phenotype** of normal and BCR/ABL-transformed myeloid progenitors.

4/9/2 (Item 2 from file: 5)

13524232 BIOSIS NO.: 200200153053

Shuttling hnRNPs as regulators of BCR/ABL leukemogenic potential.

AUTHOR: Perrotti Danilo(a); Trotta Rossana(a); Cesi Vincenzo(a); Santilli Giorgia(a); Guerzoni Clara(a); Gambacorti-Passerini Carlo; Calabretta Bruno(a)
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JOURNAL: Blood 98 (11 Part 1):p142a November 16, 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Increased survival and impaired differentiation are features of myeloid blast crisis CML cells and of myeloid precursors ectopically expressing the p210BCR/ABL oncoprotein, but the underlying mechanisms are poorly understood. Analysis of the molecular mechanism(s) which might account for the BCR/ABL-associated leukemic **phenotype** , led us to the identification of three novel regulators of BCR/ABL leukemogenic activity, the shuttling heterogeneous nuclear ribonucleoproteins (hnRNPs) FUS Embo J. (1998) 17:4442-55; Mol Cell Biol. (2000) 20:6159-69), E2 and A1. hnRNPs are RNA polymerase II-associated proteins which control the fate of eukaryotic mRNAs throughout their journey from the active site of transcription to that of translation. We show here that in myeloid progenitor cells, the deregulated BCR/ABL tyrosine kinase activity induces an increase in **hnRNP** E2 and A1 levels by preventing their ubiquitin/proteasome-dependent degradation. Expression of **hnRNP** E2 was barely detectable in mononuclear marrow cells from CML-chronic phase patients, and increases during progression into blast crisis or upon development of growth factor independence in newly established BCR/ABL-expressing cell clones. Similarly, **hnRNP A1** expression was higher in BCR/ABL-expressing myeloid progenitor cells and in primary mononuclear cells from CML-blast crisis patients than in mononuclear cells from CML-chronic phase patients. In BCR/ABL-transformed cells a) **hnRNP** E2 expression suppresses the translation of C/EBPalpha, the major regulator of granulocytic differentiation, by a mechanism dependent on the interaction with the intercistronic region contained in the 5' leader sequence of c/ebpalpha mRNA; b) expression of a **hnRNP A1** mutant defective in nuclear export was associated with suppression of growth factor-independent colony formation, reduced tumorigenic potential in vivo and downmodulation of Bcl-XL, an important survival factor for

hematopoietic cells. Together, these studies indicate that the regulation of translation by **hnRNP** E2 and of mRNA export by **hnRNP** **A1** are novel mechanisms for BCR/ABL oncogenic activity, and may provide examples of mechanisms whereby other leukemogenic proteins cause deregulated cell growth by affecting the metabolism of mRNAs encoding factors that control cell proliferation, survival and differentiation.

4/9/3 (Item 3 from file: 5)

12654888 BIOSIS NO.: 200000408390

BCR-ABL prevents c-Jun-mediated and proteasome-dependent FUS (TLS) proteolysis through a protein kinase CbetaII-dependent pathway.

AUTHOR: Perrotti Danilo(a); Iervolino Angela; Cesi Vincenzo; Cirinna Maria; Lombardini Silvia; Grassilli Emanuela; Bonatti Silvia; Claudio Pier Paolo ; Calabretta Bruno(a)
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JOURNAL: Molecular and Cellular Biology 20 (16):p6159-6169 August, 2000
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The DNA binding activity of FUS (also known as TLS), a nuclear pro-oncogene involved in multiple translocations, is regulated by BCR-ABL in a protein kinase CbetaII (PKCbetaII)-dependent manner. We show here that in normal myeloid progenitor cells FUS, although not visibly ubiquitinated, undergoes proteasome-dependent degradation, whereas in BCR-ABL-expressing cells, degradation is suppressed by PKCbetaII phosphorylation. Replacement of serine 256 with the phosphomimetic aspartic acid prevents proteasome-dependent proteolysis of FUS, while the serine-256-to-alanine FUS mutant is unstable and susceptible to degradation. Ectopic expression of the phosphomimetic S256D FUS mutant in granulocyte colony-stimulating factor-treated 32Dcl3 cells induces massive apoptosis and inhibits the differentiation of the cells escaping cell death, while the degradation-prone S256A mutant has no effect on either survival or differentiation. FUS proteolysis is induced by c-Jun, is suppressed by BCR-ABL or Jun kinase 1, and does not depend on c-Jun transactivation potential, ubiquitination, or its interaction with Jun kinase 1. In addition, c-Jun-induced FUS proteasome-dependent degradation is enhanced by heterogeneous nuclear ribonucleoprotein (**hnRNP**) **A1** and depends on the formation of a FUS-Jun- **hnRNP** **A1** -containing complex and on lack of PKCbetaII phosphorylation at serine 256 but not on FUS ubiquitination. Thus, novel mechanisms appear to be involved in the degradation of FUS in normal myeloid cells; moreover, the ability of the BCR-ABL oncoprotein to suppress FUS degradation by the induction of posttranslational modifications might contribute to the **phenotype** of BCR-ABL-expressing hematopoietic cells.

4/9/5 (Item 5 from file: 5)

12488198 BIOSIS NO.: 200000241700

The RGG domain in hnRNP **A2 affects subcellular localization.**

AUTHOR: Nichols Ralph C(a); Wang Xiao Wei; Tang Jie; Hamilton B JoNell; High Frances A; Herschman Harvey R; Rigby William F C
AUTHOR ADDRESS: (a)Section of Connective Tissue Diseases, Department of Medicine, Dartmouth Medical School, Lebanon, NH, 03756**USA

JOURNAL: Experimental Cell Research 256 (2):p522-532 May 1, 2000
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The heterogeneous nuclear ribonucleoproteins (**hnRNP**) associate with pre-mRNA in the nucleus and play an important role in RNA processing and splice site selection. In addition, **hnRNP** A proteins function in the export of mRNA to the cytoplasm. Although the **hnRNP** A proteins are predominantly nuclear, **hnRNP** **A1** shuttles rapidly between the nucleus and the cytoplasm. **HnRNP** A2, whose cytoplasmic overexpression has been identified as an early biomarker of lung cancer, has been less well studied. Cytosolic **hnRNP** A2 overexpression has also been noted in brain tumors, in which it has been correlated with translational repression of Glucose Transporter-1 expression. We now examine the role of arginine methylation on the nucleocytoplasmic localization of **hnRNP** A2 in the HEK-293 and NIH-3T3 mammalian cell lines. Treatment of either cell line with the methyltransferase inhibitor adenosine dialdehyde dramatically shifts **hnRNP** A2 localization from the nuclear to the cytoplasmic compartment, as shown both by immunoblotting and by immunocytochemistry. In vitro radiolabeling with (3H)AdoMet of GST-tagged **hnRNP** A2 RGG mutants, using recombinant protein arginine methyltransferase (PRMT1), shows (i) that **hnRNP** A2 is a substrate for PRMT1 and (ii) that methylated residues are found only in the RGG domain. Deletion of the RGG domain (R191-G253) of **hnRNP** A2 results in a cytoplasmic localization **phenotype** , detected both by immunoblotting and by immunocytochemistry. These studies indicate that the RGG domain of **hnRNP** A2 contains sequences critical for cellular localization of the protein. The data suggest that **hnRNP** A2 may contain a novel nuclear localization sequence, regulated by arginine methylation, that lies in the R191-G253 region and may function independently of the M9 transportin-1-binding region in **hnRNP** A2.

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12330109 BIOSIS NO.: 200000083611
Spatiotemporal regulation and in vitro expression of avian hnRNP A1 **, an mRNA shuttle protein-exon splicing silencer.**
AUTHOR: Bronstein Natalie(a); Kishore Ram(a); Ismail Zeinab(a); Zhang Qihang(a); Newman Stuart A(a)
AUTHOR ADDRESS: (a)New York Medical College, Valhalla, NY, 10595**USA
JOURNAL: Molecular Biology of the Cell 10 (SUPPL.):p438a Nov., 1999
CONFERENCE/MEETING: 39th Annual Meeting of the American Society for Cell Biology Washington, D.C., USA December 11-15, 1999
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01754692 ORDER NO: AADAA-I9977511
Avian hnRNP A1 **, a messenger RNA shuttle protein-exon splicing silencer: Developmental regulation and role in chondrogenesis**
Author: Bronstein, Natalie Beth
Degree: Ph.D.
Year: 2000
Corporate Source/Institution: New York Medical College (0151)
Adviser: Stuart A. Newman
Source: VOLUME 61/07-B OF DISSERTATION ABSTRACTS INTERNATIONAL. PAGE 3362. 151 PAGES
Descriptors: BIOLOGY, CELL ; BIOLOGY, GENETICS ; BIOLOGY, MOLECULAR
Descriptor Codes: 0379; 0369; 0307
ISBN: 0-599-83414-5

Post-transcriptional regulation of gene expression involves the activity of several heterogeneous nuclear RNA binding proteins (hnRNPs) proteins that mediate such functions as capping, splicing and polyadenylation of the primary transcript. hnRNPs of the A1 class have been shown to participate in the choice of mRNA splice sites in a class of

alternatively spliced mRNAs, which includes that encoding fibroblast growth factor receptor 2 (FGFR2), and to transport mature mRNAs between the nucleus and the cytoplasm. This laboratory has recently identified the unique protein of the A1 class in the chicken. Using <italic> in situ</italic> hybridization and immunohistochemistry hnRNP A1 mRNA and protein have been localized in various tissue and organ primordia of the developing chicken embryo between embryonic days 4½ and 12. Expression has been detected in the skin, heart, gizzard, liver, lung, vertebral bodies, neural tissue, intestine, kidney tubules, and developing limb cartilage. In the developing cartilage of the vertebrae and limbs hnRNP A1 protein is initially present in precartilage cell condensations and persists in early chondrocytes. <italic> In vitro</italic> studies using high density micromass cultures of limb bud precartilage mesenchyme confirm that hnRNP A1 is present in precartilage condensations, with peak values occurring just prior to cartilage differentiation. Moreover, it is upregulated coordinately with condensation formation by exogenous TGF-β, which is also an endogenous activator of this process. Work in other laboratories has shown (i) the <italic>IIIc</italic> (bek) splice form of FGFR2 is also present at sites of precartilage condensation <italic>in vivo</italic> and <italic>in vitro</italic>; (ii) in humans, mutations of <italic> FGFR2</italic> that cause missplicing of FGFR2 and expression of the <italic> IIIb</italic> (KGFR) rather than bek form of the receptor (Apert syndrome) exhibit syndactyly of fingers and toes, resulting from fusion of precartilage condensation; and (iii) hnRNP A1 is the factor that causes inclusion of F13FR2 <italic>IIIc</italic>-exon 9, leading to bek, rather than inclusion <italic> IIIb</italic>-exon 8, leading to KGFR, by a process that involves binding of hnRNP A1 to an exon splice silencer (ESS) in exon 8. Based on all these findings it is hypothesized that (i) inactivation of hnRNP A1, <underline> or</underline> (ii) competition for hnRNP A1 by an excess of FGFR2 exon 8 mRNA, should each lead to missplicing of FGFR2. These predictions have been tested by electroporating chick leg bud cells, which normally differentiate into well separated nodules of cartilage, with either antisense RNA directed against hnRNP A1, or sense RNA corresponding to FGFR2 exon 8. In both cases the cultures formed a continuous sheet of cartilage resulting from fusion of precartilage condensations. Western blot analysis of hnRNP A1 protein production confirmed that it was substantially reduced in antisense-transfected cultures, but not in sense-transfected cultures. These results represent an <italic>in vitro</italic> analogue of Apert syndrome, suggesting that FGFR2 was misspliced in both experiments. Treatment of a 6 day embryo with antisense hnRNP A1 transcript also lead to a forelimb defect with increased cartilage formation detected in the stylopod and malformed skeletal elements in the zeugopod and autopod.